Update on Safety of Herpes Zoster Vaccine

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
Atlanta, GA
June 27-28, 2007

Sandra Chaves, MD, MSc
Division of Viral Diseases
Centers for Disease Control and Prevention

Zostavax® [Zoster Vaccine, Live (Oka/Merck)]

- **May 2006 - FDA license issued for adults age 60 years and older**
- **Oct. 2006 - ACIP recommended for adults age 60 years and older**

- **Indication**: Prevention of herpes zoster

- **Dosage:** 0.65-mL given once (subcutaneous)

  Each dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck strain of VZV

Pre-licensure Safety - Zostavax®

- Transient injection-site reactions occurred more frequently among vaccine recipients

- No clinically important differences between vaccine and placebo recipients with respect to:
  - Systemic clinical adverse experience
  - Serious adverse experience

- **Note:** In the Adverse Event Monitoring Substudy, the rate of serious AEs was higher among vaccine recipients than placebo recipients (~6,000 subjects) – 1.9% vs. 1.3% in vaccine and placebo recipients respectively; P=0.03. No specific pattern observed

*Oxman *et al.* NEJM 2005; package insert 2006

VAERS: Post-licensure Safety of Zostavax®

- National post-licensure safety surveillance system jointly operated by CDC and FDA
- Spontaneous reporting submitted by clinicians, manufacturers, patients/parents, others
  - Subject to well described limitations of passive surveillance
- Medical Dictionary for Regulatory Activities (MedDRA) used for coding (replaced COSTART in January 2007)
- Serious reports according to U.S. regulatory and international criteria
  - Hospitalization, death, “life-threatening” or “disabling” illness, other medically important conditions

VAERS – through June 1, 2007

- 590 reports*
  - Overall reporting rate: **73.3/100,000 doses distributed†**
- 44/590 classified as serious
  - Serious reporting rate: **5.5/100,000 doses distributed†**
- 2/44 deaths
  - Death reporting rate: **0.2/100,000 doses administered†**

* Each report may contain more than one event

† Dose distribution data obtained from vaccine manufacturer

VAERS – through June 1, 2007

Demographics (N=590 reports)

Category		All Reports N (%)	Serious N (%)
Sex	Female	375 (63.6)	26 (59.1)
	Male	174 (29.6)	16 (36.4)
	Unk	41 (6.8)	2 (4.5)
Age group	<60 yrs	82 (13.9)	1 (2.3)
	60-69 yrs	202 (34.3)	11 (25.0)
	70-79 yrs	134 (22.7)	19 (43.2)
	80+	54 (9.1)	6 (13.6)
	Unk	118 (20.0)	7 (15.9)

VAERS – through June 1, 2007

Possible Off-label use or Administration error:

- **Age group <60 years (N=82)**

<1 year	5 (6%)
1 year	16 (19%)
5 to 20 years	21 (26%)
21 to 59 years	40 (49%)

Vaccines administered concomitantly with Zostavax

- 90% (531/590) of all reports refer to administration of Zostavax alone
- The remainder (59/590) refer to concomitantly administration of other vaccines (e.g., DTaP, IPV, MMR, Hepa, FLU, PNC)

VAERS - Most Frequent and Selected Adverse Events* (Based on 590 reports)

Event	Serious (N=315) n(%)	All events (N=1526) n(%)
Injection site reaction	10 (3.2)	307 (20.1)
Any rash	9 (2.8)	177 (11.6)
Herpes Zoster	13 (4.1)	145 (9.5)
Medication error		60 (3.9)
Pyrexia	4 (1.2)	31(2.0)
Headache		27 (1.7)
Urticaria	1(0.3)	19 (1.2)
Varicella /Varicella postvaccination	3(0.9)	16 (1.0)
Secondary Transmission		8 (0.5)
Arthralgia		6 (0.3)
Encephalitis	2 (0.6)	3 (0.1)
Idiopathic Thrombocytopenic Purpura	2 (0.6)	3 (0.1)
Anaphylactic reaction	1(0.3)	1(0.0)

*Events coded based on MedDRA – not individual reports. Note that categories are not mutually exclusive

VAERS – Most Frequent Adverse Events

Injection site reaction (n= 307)

- 83% female
- Age – Median 65 years (range: <1 to 88 years)
- Onset interval – Median 1 day (range: <1 to 254 days)

Any Rash (n=177)

- 57% female
- Age – Median 67 years (range: 1 to 89 years)
- Onset interval – Median 3 days (range: <1 to 372 days)

Herpes Zoster* (n=145)

- 61% female
- Age – Median 68 years (range: <1 to 91 years)
- Onset interval – Median 5 days (range: <1 to 209 days)

*Include 1 HZ ophthalmic.

Note: No Oka strain identified so far among HZ samples tested

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Selected non-fatal reports
VAERS – through June 1, 2007

Allergic Reaction/Anaphylaxis

Case#1: 71 yo, M, few hours after vaccination felt dizzy, nauseated, numbness in arm, vertigo. Hospitalized for 24 hours. Fully recovered.

Case#2: 79 yo. F, the day after vaccination developed Flu-like symptoms and throat spasm. Hospitalized for 24 hours. Fully recovered.

Case#3: 76 yo, F, few hours after vaccination experienced an anaphylactic reaction described as “racing heart, throat spasm and tightness of neck”. Hospitalized for 24 hours, administered IV famotidine and IV steroids. Fully recovered.

Selected non-fatal reports
VAERS – through June 1, 2007

Pregnancy (N=1)

Case#1:39 yo, F, ten days after vaccination had a positive pregnancy test. No information available regarding outcome of pregnancy. Patient being f/up by the Pregnancy Registry.

Note: Patient requested vaccination, not medical error

Encephalitis (N=3)

Case#1:75yo, M, within 24 hours of vaccination developed neck pain, disorientation, erratic driving. Hospitalized. Magnetic resonance imaging of brain showed no acute infarct. CSF PCR for herpes simplex negative.

Case#2:Age unk, M, 10 days after vaccination developed encephalitis. No other info.

Case#3: 60yr, M, 3 months after vaccination developed encephalitis. No other info.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Selected non-fatal reports
VAERS – through June 1, 2007

Secondary Transmission (N=8)

- 5 reports of persons developing zoster after exposure to spouses who had been vaccinated with Zostavax
- Child exposed to grandparents a few days after they had been vaccinated and developed chickenpox. No more information.
- Man exposed to his wife who was vaccinated with Zostavax. Ten days later he developed chickenpox. No more information
- Physician exposed to patient who developed zoster after vaccination with Zostavax. Two weeks later physician developed 2 vesicular lesions at dermatome C8. The physician had history of chickenpox as child. She started valacyclovir.

Selected non-fatal reports
VAERS – through June 1, 2007

Varicella and Varicella post-vaccination

- 11 reports where varicella-like rash occurred after vaccination with Zostavax
  - 1 case was hospitalized due to extent of rash (no other info)

- 4 reports coded as 'varicella post-vaccination', but they were all described as zoster lesions occurring after receipt of Zostavax

  - Female, 63 year old, months (?) after vaccination with Zostavax was hospitalized with acute retinal necrosis and herpes zoster in right eye

Selected non-fatal reports
VAERS – through June 1, 2007

Medication error/Wrong drug administered

- Used instead of Varivax (34 reports; 21 in children <12 years)
- Used instead of ProQuad (7 reports)
- Used instead of Gardesil (5 reports)
- Used instead of MMR II
- Diluted with other vaccines (administered in children)
- Given to immunosuppressed individuals (2 reports; both >70 years)
- Accidental eye exposure to vaccine during preparation
- Possible off-label use (47 yo and 53 yo, both reported due to local injection reaction)

Deaths following Zostavax
VAERS through June 1 2007

- CASE #1: 83 yo, F, who was vaccinated 6 months previously. Subsequently the patient developed zoster. Cause of death stated as sepsis and right lower lobe pneumonia.

- CASE #2: 80 yo, female, vaccinated on April 3, 2007. Within a week the patient died from a heart attack. Cause of death stated as inferior myocardial infarction.

Summary: Zoster vaccine post-licensure safety

- Most frequently reported events: injection site reaction, rash, and herpes zoster
  - No HZ due to Oka strain identified (but very few tested)
- Challenging surveillance due to high prevalence of co-morbid conditions among those ≥60 years – anticipated coincidental AEs
- Administration errors occurred in adults and children. Difficult to assess off-label use
- VAERS data: Subject to underreporting, limited clinical and laboratory information to establish causality, lack of denominator data
- Post-licensure safety studies expected to be undertaken

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Post-licensure Safety Studies

- **Vaccine Safety Datalink (VSD) Project (ISO/CDC)**
  - Kaiser Permanente (Northern California and North West, Portland), and Group Health Cooperative, Seattle - Over 1 million enrollees.
  - Vaccination and medical records from adults age 50+ years including inpatient, outpatient, and emergency department

- **Merck's commitment**
  - Randomized placebo-controlled safety study with up to 6 months of follow-up (for rates of serious AEs)
  - Observational study in a US HMO (to detect potential signals)
  - Assess safety of a high potency dose of Zostavax (based on observational study)
  - Randomized placebo-controlled, double blind study to assess safety of Zostavax in subjects receiving low-to-moderate doses of corticosteroids (~ 5 to20 mg/day of prednisone)

Acknowledgments

ISO

- Kimp Walton
- Beth Hibbs
- Penina Harber
- Karen Broder
- Paul Gargiullo on behalf of the VSD Zoster Vaccine Safety Studies Workgroup

NCIRD

- Rafael Harpaz
- Jane Seward

FDA

- Manette Niu
- Jane Woo
- Robert Ball
- Miles Braun

Thank you

“We don't stop playing because we grow old. We grow old because we stop playing.”

-George Bernard Shaw